

REMARKS

In response to the Notice of Non-Compliant Amendment mailed November 13, 2008, Applicants have corrected the status identifiers of claims 110 and 112 to read “canceled”. Applicants have corrected the claim numbers in the following paragraph, and otherwise re-submit the amendment dated October 10, 2008.

Claims 1-106, 108-110, 112 and 114 are canceled, and claims 107, 111, 118 and 119 have been amended. Claims 107, 111, 113 and 115-119 are now pending for the Examiner’s consideration.

Claims 107, 111, 118 and 119 have been amended to recite that the formulation has a bulk density of at least about 0.50 kg/L, as recited in claim 114, now canceled. No new matter is added.

Applicant respectfully requests favorable consideration of the pending claims.

Claims 107, 111 and 113-119 were rejected under 35 U.S.C. § 103(a) as being anticipated by International Application Publication WO 01/37820 (“Shenoy”), for the reasons set forth on pages 3-9 of the Office Action. Applicant respectfully traverses.

By the present amendments, each independent claim now recites that the formulation has a bulk density of at least about 0.50 kg/L, as previously recited in claim 114, now canceled. Applicants therefore address the rejection as applied to claim 114.

The Examiner argues that it would have been obvious to use the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide in the formulations of Shenoy, and at the specific concentrations claimed, simply because Shenoy discloses broad ranges of concentrations that generically encompass the specifically claimed ranges, Shenoy discloses hundreds of compounds, including the free base of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide, and Shenoy discloses numerous possible salts of such compounds. Applicants disagree that one skilled in the art would be motivated to select the specifically claimed compound, 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide, select a specific salt of that compound, L-malate, and further

select the specifically claimed amounts from among the nearly limitless ranges shown, for example, on pages 92-93 of Shenoy.

Further, as presently claimed, the resulting compositions have a bulk density of at least about 0.50 kg/L. With regard to the bulk density, the Examiner argues that the compositions of Shenoy would inherently possess this property. However, as set forth in MPEP 2112, “the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic” (citing *In re Rijckaert*). The missing characteristic must be “necessarily present” in the prior art. “Inherency, however, may not be established by probabilities or possibilities” (quoting *In re Robertson*). The Examiner has merely alleged that the claimed bulk density would be present in the Shenoy compositions if the proper components and ranges are selected. It is not incumbent upon Applicants to make and test each prior art formulation of Shenoy, nor to pick a hypothetical formulation created by picking and choosing components and ranges as the “closest” formulation. In order to rebut the Examiner’s allegation that the claimed bulk density would be inherent in the Shenoy formulations, Applicants must merely show that the bulk density is not “necessarily present” in the prior art. Applicants submit that the present specification already establishes that such bulk density is not inherent.

For example, in Example 1 of the present specification, a formulation is shown using the presently claimed compound, 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide, in free base form, at a concentration of 65% w/w—a compound and concentration that are apparently within the scope of the Shenoy disclosure as interpreted by the Examiner. This formulation, however, has a bulk density of only 0.44 to 0.46 kg/L, despite the superficial similarities to the claimed formulation. If indeed it is fair to pick and choose compounds, salts and concentrations from within the broad Shenoy disclosure, then this “prior art” composition would necessarily possess the claimed bulk density of at least about 0.50 kg/L, which it clearly does not. Applicants submit that the art is sufficiently unpredictable that it is not possible to assert, a priori, that the bulk density of particular compositions is necessarily high enough to read on the claimed property.

As a further example, Example 5 of the present specification shows a composition of a compound, 5-[(Z)-(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-N-[2-hydroxy-

3-morpholin-4-ylpropyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide, in the form of a maleate salt. Applicants note that this compound is not disclosed in Shenoy, but differs from the compound of the present claims only in the substituent on the amide chain. As shown in Example 5, this compound was formulated as in Examples 1-4, but showed a bulk density of only about 0.05 to 0.07 kg/L, or about one-tenth of the bulk density required by the present claims. Although this compound is not in the Shenoy reference, Applicants believe the dramatic difference in bulk density, despite having the same formulation, is compelling evidence that the art is unpredictable, and it is unreasonable to suppose that the property of having a bulk density of at least about 0.50 kg/L as recited in the present claims is an inherent property that is necessarily present in the compositions of Shenoy.

Finally, the Examiner discounts the Comparative Example, which shows the superior properties of a composition as claimed compared to a similar composition having a higher concentration of active ingredient, 75%. The Examiner argues that Applicants failed to compare the claimed composition to the closest prior art composition. However, the comparison is between a composition of the same active ingredient, in the same salt form, but having the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide present in an amount of 75% versus 40%. As discussed above, using the free base compound gives a bulk density that is undesirably low, using a different compound also has a bulk density that is too low, and even using the correct compound and salt, but at a higher concentration, gives a composition that has undesirable sticking problems in the manufacturing process. The Comparative Example further illustrates that the art is unpredictable, and one skilled in the art would not be motivated to pick and choose compounds, salts, and concentrations from the prior art with any reasonable expectation of success.

Accordingly, Applicants respectfully request that the rejection of the pending claims over the Shenoy reference be withdrawn.

Applicant believes all claims are now in condition for allowance. Should there be any issues that have not been addressed to the Examiners satisfaction, Applicant invites the Examiner to contact the undersigned attorney.

If any fees other than those submitted herewith are due in connection with this response, including the fee for any required extension of time (for which Applicant hereby petitions), please charge such fees to Deposit Account No. 161445.

Respectfully submitted,

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